

## NEUROSCIENCES AND NEUROANAESTHESIA

# Bispectral and spectral entropy indices at propofol-induced loss of consciousness in young and elderly patients

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**Background.** Bispectral (BIS) and state/response entropy (SE/RE) indices have been widely used to estimate depth of anaesthesia and sedation. In adults, independent of age, adequate and safe depth of anaesthesia for surgery is usually assumed when these indices are between 40 and 60. Since the EEG is changing with increasing age, we investigated the impact of advanced age on BIS, SE, and RE indices during induction.

**Methods.** BIS and SE/RE indices were recorded continuously in elderly ( $\geq 65$  yr) and young ( $\leq 40$  yr) surgical patients who received propofol until loss of consciousness (LOC) using step-wise increasing effect-site concentrations. LOC was defined as an observer assessment of alertness/sedation score  $< 2$ , corresponding to the absence of response to mild prodding or shaking.

**Results.** We analysed 35 elderly [average age, 78 yr (range, 67–96)] and 34 young [35 (19–40)] patients. At LOC, all indices were significantly higher in elderly compared with young patients: BIS<sub>LOC</sub>, median 70 (range, 58–91) vs 58 (40–70); SE<sub>LOC</sub>, 71 (31–88) vs 55.5 (23–79); and RE<sub>LOC</sub>, 79 (35–96) vs 59 (25–80) ( $P < 0.001$  for all comparisons). With all three monitors, only a minority of elderly patients lost consciousness within a 40–60 index range: two (5.7%) with BIS and RE each, and seven (20%) with SE. In young patients, the respective numbers were 20 (58.8%) for BIS, 13 (38.2%) for SE, and nine (26.5%) for RE.

**Conclusions.** In adults undergoing propofol induction, BIS, SE, and RE indices at LOC are significantly affected by age.

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In daily clinical practice, processed, non-invasive, EEG monitors such as the bispectral index (BIS) or spectral entropy (state/response, SE/RE) are increasingly used to estimate depth of sedation and anaesthesia. These monitors provide a single numerical value ranging from 100 (fully awake) to 0 (deepest level of sedation), and they are now well established to predict loss of consciousness (LOC) and to estimate depth of sedation in surgical patients undergoing i.v. or inhalation anaesthesia.<sup>1 2</sup> The recommended and widely accepted range of values for adequate depth of anaesthesia for surgery is 40–60 in these two monitors. No manufacturer has so far validated a range of ages for which that recommended range of values

ensured adequate anaesthesia, although the pattern of the EEG is changing with increasing age.<sup>3</sup> In the elderly, modifications can be observed in the awake and in the sleep state, and during anaesthesia. For instance, during propofol anaesthesia, EEG amplitudes are smaller in the elderly compared with younger patients.<sup>4</sup> It would be useful to know whether indices of processed EEG monitors also differed between younger and elderly patients undergoing sedation and anaesthesia, and whether such differences were clinically relevant. In adults undergoing sevoflurane sedation, increasing age was shown to reduce sevoflurane requirements to suppress the response to a verbal command, but did not change the BIS index that

was associated with this endpoint.<sup>5</sup> Similar data from patients undergoing propofol induction are lacking.

The objective of this observational study was to investigate whether at the time point of propofol-induced LOC, BIS and SE/RE indices differed between young and elderly patients, and to quantify these differences.

## Methods

The study was approved by the ethics committee of the University Hospitals of Geneva. After having obtained written informed consent, 'young' ( $\leq 40$  yr) and 'elderly' ( $\geq 65$  yr) patients, ASA I–III, undergoing elective surgery requiring general anaesthesia, were included. The choice of the age ranges was based on a previously published, similar study.<sup>5</sup> We did not consider patients with significant cardiorespiratory or other end-organ diseases, depression or other psychiatric disorders, dementia, history of oesophageal reflux or hiatus hernia, drug or alcohol abuse, or significant obesity (BMI  $> 30$ ).

Patients did not receive any premedication. Monitoring included a three-lead electrocardiograph, peripheral pulse oxymetry, and end-tidal carbon dioxide ( $E'_{CO_2}$ ). Systolic and diastolic arterial pressure and heart rate were recorded. Patients had a venous catheter inserted on the back of a hand and a Ringer's lactate infusion connected to it. They were spontaneously breathing oxygen 4 litre  $\text{min}^{-1}$  through a facemask.

### Propofol administration

The study period lasted from the start of propofol administration until LOC (definition of LOC, see below: clinical evaluation of depth of sedation). No other drugs were administered during the study period.

Propofol was administered using a commercially available target-controlled infusion system with an incorporated pharmacokinetic model (Base Primea, Fresenius-Vial, Brezins, France).<sup>6, 7</sup> The induction procedure until LOC was strictly controlled. Propofol effect-site concentrations were increased in  $0.5 \mu\text{g ml}^{-1}$  steps. After each  $0.5 \mu\text{g ml}^{-1}$  increase, equilibration between plasma and effect-site concentrations, as recorded on the screen of the syringe driver, was awaited and was kept unchanged for 5 min. Subsequently, the next higher effect-site concentration was targeted. This procedure was repeated until LOC.

When patients showed signs of hypoventilation before LOC (pulse oxymetry  $< 95\%$ ,  $E'_{CO_2} > 6$  kPa, or both), ventilation was gently manually assisted using oxygen 10 litre  $\text{min}^{-1}$  through the facemask. All induction procedures were performed by a trained anaesthesiologist.

### Clinical evaluation of depth of sedation

Depth of sedation was evaluated by an independent observer (C.L.) using the 0–5-point observer assessment of

**Table 1** OAA/S scale.<sup>8</sup> A score of 5 corresponded to an awake patient; a score  $< 2$  was regarded as LOC

Responds readily to name spoken in normal tone	5
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly, repeatedly, or both	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

alertness/sedation (OAA/S) scale (Table 1).<sup>8</sup> An OAA/S score of 5 corresponded to a fully awake patient. An OAA/S score  $< 2$  (absence of response to mild prodding or shaking) was regarded as LOC. As soon as the patient lost consciousness, the study was terminated. Subsequently, the patient received an opioid and a non-depolarizing neuromuscular blocking agent i.v., the trachea was intubated and the patient underwent the scheduled surgical procedure.

### Processed EEG monitors

Electrodes for BIS and SE/RE were placed on the patient's forehead as recommended by the manufacturers. The side of electrode placement (left or right temporal) was chosen at random. For BIS (XP™ version 3.3, A2000 with XP upgrade 186–0125), we used a sensor XP electrode (Aspect Medical System, MA, USA). Electrode impedance was kept below 5 k $\Omega$ . The index was calculated and displayed continuously using an Aspect A-2000 XP monitor (Aspect Medical System). The smoothing time was set at 15 s. Original entropy electrodes (GE Healthcare, Helsinki, Finland) were used to register SE/RE. Electrode impedance was kept below 7.5 k $\Omega$ . SE and RE were computed and displayed continuously using an S/5 M-entropy Module (GE Healthcare).

### Data recording

OAA/S score and indices of BIS, SE, and RE were recorded at baseline (i.e. before drug administration, awake patient in the supine position and eyes closed, quiet environment), and at the end of each steady state immediately before the subsequent increase in propofol effect-site concentration. Indices were computed as averaged values observed during a period of 30 s. To avoid missing the time point of LOC, OAA/S scores were assessed every 2 min (i.e. independent of the stepwise increase in propofol effect-site concentrations) as soon as the score had decreased to 4. To minimize interactions between verbal or tactile stimulation and BIS, SE, and RE values, indices were always recorded before OAA/S score assessment. Painful stimuli, for instance, trapezius squeeze, were not applied.

Arterial pressure and heart rate were measured before (baseline) and every 5 min during propofol administration until LOC. Arterial hypotension was defined as a decrease in systolic arterial pressure  $\geq 20\%$  when compared with

baseline. Bradycardia was defined as a heart rate  $<45$  beats  $\text{min}^{-1}$ .

### Power calculation and statistical analyses

The strength of the association between age and BIS and entropy indices was largely unknown when we designed our study. We considered that an age-related difference of 15 units of average indices at LOC (for instance, a change from 75 to 60) would be clinically relevant, and we assumed a similar variability in the two age groups (assumed SD, 20). A sample size of 32 patients in each group was needed to achieve 85% power to detect this difference, if present. We recruited 35 patients per group to allow for drop-outs.

Indices at LOC ( $\text{BIS}_{\text{LOC}}$ ,  $\text{SE}_{\text{LOC}}$ , and  $\text{RE}_{\text{LOC}}$ ) and patient characteristics were described by percentages for categorical variables and by means (SD) and medians (with inter-quartile range) for numerical variables.

To estimate  $\text{BIS}_{95}$ ,  $\text{SE}_{95}$ , and  $\text{RE}_{95}$  (i.e. indices at which 95% of patients lost consciousness), we computed the 5th percentiles of the distribution of individual values for each index. Each index was compared between young and elderly patients using a Mann–Whitney test. Multivariate analyses (linear regression) were performed to check differences in the indices with adjustment for gender, body weight and size, and smoking status. The adjustment included smoking status since it was shown to influence both the hypnotic efficacy of propofol and BIS.<sup>9</sup> The assumption of normality and the goodness-of-fit were checked.

To compare proportions of young and elderly patients that were within the conventionally recommended index range at LOC (i.e. between 40 and 60), we categorized indices into three subgroups of index ranges:  $\leq 39$ , 40–59, and  $\geq 60$ . Proportions were compared using Fisher's exact test.

All analyses were performed using the Statistical Package for Social Sciences (version 15, SPSS Inc., Chicago, IL, USA). A  $P$ -value of  $<0.05$  was considered statistically significant.

## Results

Seventy patients were included. Data from one young patient were excluded since she received benzodiazepine as a premedication. Thus, we eventually analysed data from 35 elderly and 34 young patients. Young patients were on average 35 yr old; elderly patients had a mean age of 78 yr (Table 2). Young patients were significantly taller than elderly patients. Gender distribution and average body weights were similar in both groups. Percentages of smokers were also similar in both groups. Eight young and seven elderly patients needed ventilatory assistance before LOC; in all, OAA/S score was 3, when assistance was commenced. In these patients, gentle,

**Table 2** Patient characteristics. \* $\chi^2$  test; \*\*Mann–Whitney test. N/A, not applicable

	Young ( $n=34$ )	Elderly ( $n=35$ )	$P$ -value
Gender (male/female)	19/15	19/16	0.89*
Age (yr) mean (SD) (min, max)	35 (5.2) (19, 40)	78 (6.7) (67, 96)	N/A
Height (cm) mean (SD)	173 (9.3)	166 (8.8)	0.001**
Weight (kg) mean (SD)	76 (10.3)	71 (12.3)	0.07**
Smokers $n$ (%)	10 (29)	7 (20)	0.36*

manually assisted ventilation through the facemask was performed and this was sometimes associated with transitory increases in EEG indices.

### Indices at LOC

For all three EEG monitors, LOC occurred at significantly higher indices in elderly compared with young patients (Fig. 1 and Table 3). Median  $\text{BIS}_{\text{LOC}}$  was 70 (range, 58–91) in the elderly compared with 58 (range, 40–70) in the young; median  $\text{SE}_{\text{LOC}}$  was 71 (range, 31–88) in the elderly compared with 55.5 (range, 23–79) in the young; median  $\text{RE}_{\text{LOC}}$  was 79 in the elderly (range, 35–96) compared with 59 (range, 25–80) in the young ( $P<0.001$  for all comparisons, Mann–Whitney test). These differences were still significant in the multivariate analyses ( $P<0.001$  for all comparisons).

Indices at which 95% of patients had lost consciousness (i.e.  $\text{BIS}_{95}$ ,  $\text{SE}_{95}$ , and  $\text{RE}_{95}$ ) were also consistently and significantly higher in the elderly compared with young patients (Table 3); for BIS, the difference in the 5th percentiles between elderly and young was 18 units, for SE was 16 units, and for RE was 14.3 units ( $P<0.001$  for all comparisons, Wald test).

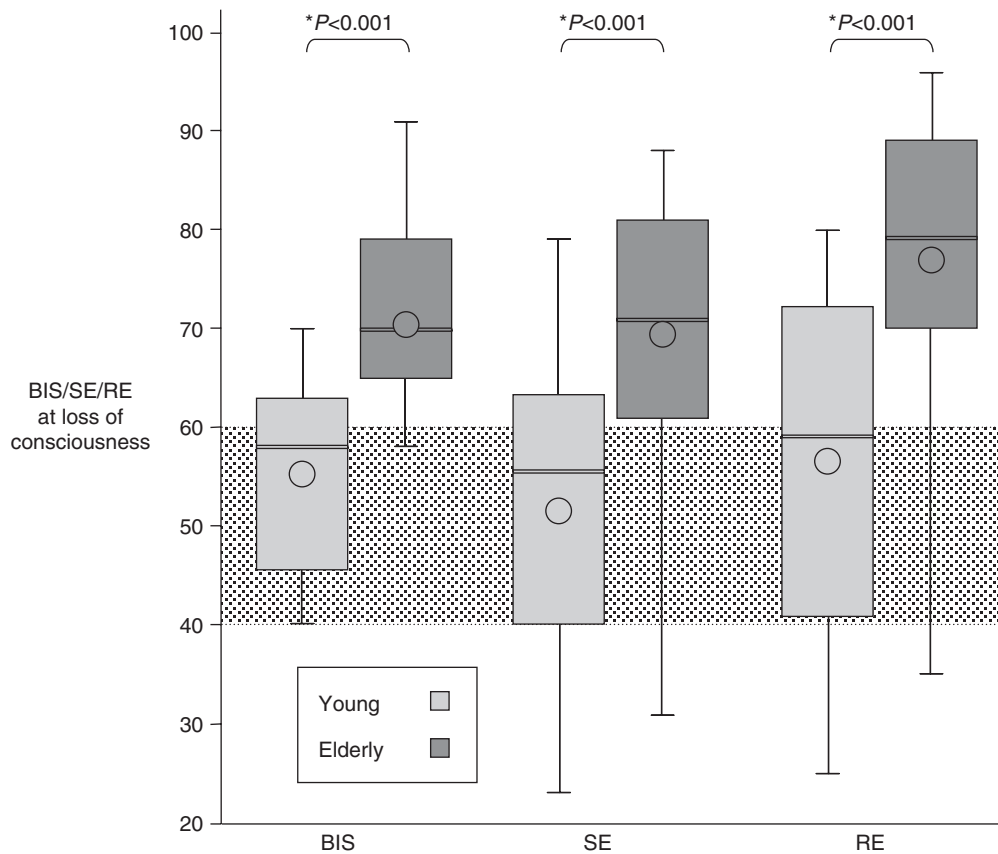
### Adequacy of the 40–60 index range

The number of patients who lost consciousness within the three predefined index ranges ( $\leq 39$ , 40–59, and  $\geq 60$ ) was significantly different between young and elderly for all three monitors (Table 4 and Fig. 1).

Most elderly patients lost consciousness at indices of  $\geq 60$  ( $\text{BIS}$  94.3%,  $\text{SE}$  77.1%, and  $\text{RE}$  91.4%). Only two (5.7%), seven (20%), and two (5.7%) elderly patients, respectively, had a BIS, SE, or RE index between 40 and 59 at LOC. In comparison, the number of young patients who lost consciousness at indices between 40 and 59 was 20 (58.8%) for BIS, 13 (38.2%) for SE, and nine (26.5%) for RE.

### Comparison of the three monitors

Variability in indices at LOC was smaller with the BIS monitor compared with the SE and RE monitors in both young and elderly patients. This was mainly due to a larger number of young and elderly patients who eventually lost consciousness at SE and RE indices of  $\leq 39$



**Fig 1** BIS, SE, and RE at LOC in young ( $\leq 40$  yr,  $n=34$ ) and elderly ( $\geq 65$  yr,  $n=35$ ) patients. The top, bottom, and line through the middle of the boxes correspond to the 25th percentile, 75th percentile, and median respectively; the circles are means. The whiskers extend from the minimum to the maximum value (data, see Table 3). The grey shading covers the recommended range of indices for adequate depth of anaesthesia (i.e. 40–60). \* $P$ -values from multivariate analysis (linear regression).

**Table 3** Indices of BIS, SE, and RE at LOC in young and elderly patients. Data to box and whiskers plots as shown in Figure 1. IQR, inter-quartile range (25th to 75th percentile)

	Bispectral index		State entropy		Response entropy	
	Young ( $\leq 40$ yr) $n=34$	Elderly ( $\geq 65$ yr) $n=35$	Young ( $\leq 40$ yr) $n=34$	Elderly ( $\geq 65$ yr) $n=35$	Young ( $\leq 40$ yr) $n=34$	Elderly ( $\geq 65$ yr) $n=35$
Mean	55.1	70.7	51.9	69.2	56.8	77.0
Median	58.0	70.0	55.5	71.0	59.0	79.0
Range (min–max)	40.0–70.0	58.0–91.0	23.0–79.0	31.0–88.0	25.0–80.0	35.0–96.0
5th percentile	40.8	58.8	23.8	39.8	29.5	43.8
IQR	45.8–63.0	65.0–79.0	40.0–63.3	61.0–81.0	41.0–72.3	70.0–96.0
95th percentile	67.8	87.8	74.5	87.2	79.3	96.0

(Table 4). In contrast, with BIS, all patients lost consciousness with an index of  $\geq 40$ . Indices of BIS, SE, and RE were significantly different in the elderly ( $P=0.01$ , Kruskal–Wallis test) but were not in young patients ( $P=0.37$ , Kruskal–Wallis test).

### Haemodynamics

Twenty elderly compared with 10 young patients presented at least one episode of hypotension, a difference that was statistically significant ( $P<0.037$ ,  $\chi^2$  test with Yates’

continuity correction). None of the patients had an episode of bradycardia.

### Discussion

Our study showed that at LOC during propofol induction, indices of all tested EEG monitors were clearly higher in elderly compared with young patients. Indices at which 95% of patients had lost consciousness (i.e. BIS<sub>95</sub>, SE<sub>95</sub>, and RE<sub>95</sub>) differed by about 15 u.

**Table 4** Number of young and elderly patients who lost consciousness at three different ranges of indices

Range of indices	Bispectral index				State entropy				Response entropy			
	Young ( $\leq 40$ yr) <i>n</i> =34		Elderly ( $\geq 65$ yr) <i>n</i> =35		Young ( $\leq 40$ yr) <i>n</i> =34		Elderly ( $\geq 65$ yr) <i>n</i> =35		Young ( $\leq 40$ yr) <i>n</i> =34		Elderly ( $\geq 65$ yr) <i>n</i> =35	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
39 or less	0	0.0	0	0.0	8	23.5	1	2.9	8	23.5	1	2.9
40–59	20	58.8	2	5.7	13	38.2	7	20.0	9	26.5	2	5.7
60 or more	14	41.2	33	94.3	13	38.2	27	77.1	17	50.0	32	91.4
	<i>P</i> <0.01 (Fisher's exact)				<i>P</i> <0.01 (Fisher's exact)				<i>P</i> <0.01 (Fisher's exact)			

Several factors may have contributed to this age-related difference. It is well known that EEG pattern changes with increasing age. In the elderly, a decrease in the dominant frequency within the alpha band compared with middle-aged persons has been described.<sup>10</sup> Age-related changes in EEG parameters have also been observed during propofol anaesthesia; elderly patients ( $>70$  yr) presented smaller total power of the EEG when compared with younger patients ( $<50$  yr).<sup>4</sup> In the same study, elderly patients reached significantly deeper EEG stages during standardized propofol induction (2 mg kg<sup>-1</sup> over 1 min), when compared with younger patients.<sup>4</sup> The biologic basis of these age-dependent EEG changes remains unknown, although a reduction of the synaptic density in the cortex and a reduced synchronization of cortical cells are potentially contributing factors. It has been suggested that for reliable classification of the complex EEG signal, a multivariable approach accounting for age effects should be used.<sup>4</sup>

Algorithms for BIS and spectral entropy calculations are sophisticated and they are largely covert. Unfortunately, the precise algorithm that is used for computing the BIS index is not in the public domain, and therefore, decisive conclusions cannot be drawn. Apparently, the index was calculated from EEG subparameters and the coefficients were obtained from multivariate analyses of an EEG database.<sup>11</sup> However, information about subjects who were used to create that EEG database, for instance, their age, is lacking. Contrary to BIS, the mathematics that underlie spectral entropy have been published,<sup>12</sup> and it is obvious that age was not considered for that model. Our data and data from others<sup>4</sup> strongly suggest that independent of study design and EEG monitor, advanced age should be taken into consideration when propofol is used for induction.

Our study has several limitations. First, our model may be regarded as an oversimplification of clinical reality. The data were generated at LOC during slow propofol induction and before surgical stimulation. That setting cannot necessarily be extrapolated to patients receiving a different hypnotic, a combination of drugs, or those undergoing surgery. Katoh and colleagues<sup>5</sup> used sevoflurane in a similar study and they reported different results. In their study, elderly patients (65–85 yr) needed lower end-tidal

sevoflurane concentrations for LOC than did young (18–39 yr) or middle-aged (40–64 yr) patients; however, BIS indices at LOC did not differ among the three age groups. This raises the question as to whether age-related EEG changes depended on the hypnotic. It has been reported that BIS indices were significantly different depending on whether patients were sedated with sevoflurane or propofol.<sup>13</sup> When propofol or sevoflurane was used to try to identify quantitative EEG variables that reliably reflected sedation levels and LOC, propofol tended to cause a greater frontal alpha predominance than did sevoflurane.<sup>14</sup> Interestingly, quantitative EEG techniques<sup>14</sup> take into account age-related EEG variability. Additionally, in daily clinical practice, surgical patients almost always receive several concomitant hypnotic drugs, for instance, premedication with a benzodiazepine and a strong opioid intraoperatively, and these are likely to interact with the hypnotic properties of propofol. The capacity of the BIS in predicting conscious and unconscious states further decreased when a combination of sevoflurane or propofol and opioid was used.<sup>15</sup> Opioids were shown to enhance depth of propofol-induced sedation, although the BIS monitor was unable to show this.<sup>16</sup> In our study, no concomitant drugs were used. Finally, it would be interesting to repeat our study but to extend observations into the early surgical period, looking out for potential differences in indices during administration of i.v. analgesics and neuromuscular blocking agents, and to study the impact of painful stimulation.

A second issue that may limit the applicability of our results is the capability of processed EEG monitors to assess unconsciousness. Katoh and colleagues,<sup>5</sup> for instance, showed that BIS was a better predictor of LOC than was end-tidal sevoflurane concentration. However, during propofol administration, BIS indices showed a high correlation with propofol target concentrations, whereas the discrimination between conscious and unconscious state was less than ideal.<sup>15</sup> On the basis of our results, we can clearly postulate that age is yet another confounding factor that influences the relationship between BIS index and conscious/unconscious state.

Thirdly, EEG indices (particularly BIS and RE) are very sensitive to EMG activity. This may be especially true during superficial levels of sedation and in the



absence of muscle relaxation. EMG activity can increase an EEG index regardless of the sedation level. We cannot exclude that some contamination happened in our patients and it may partially explain why 90% of the elderly patients lost consciousness when their BIS and RE indices were still  $\geq 60$  but only 77% lost consciousness when their SE index was  $\geq 60$  (Table 4).

Fourthly, we used the OAA/S scale to diagnose LOC. That tool is based on a progressive mode of stimulation, ranging from verbal stimuli to physical shaking and moderate noxious stimuli.<sup>8</sup> Subjective methods remain a potential source of observer bias. For instance, in elderly patients, the observer may have unconsciously applied tactile and verbal stimuli that were less intensive. Alternatively, the observer may have expected some degree of hearing loss in the elderly and, consequently, may have used more intense verbal stimuli. In our study, one single investigator performed all assessments to minimize inter-observer variability. Also, the endpoint LOC in the OAA/S scale is not clearly defined. We arbitrarily defined LOC as loss of response to mild prodding and shaking (i.e. OAA/S score  $< 2$ ). Others have used the same scale, but a different cut-off for LOC.<sup>5</sup>

Fifthly, some patients needed ventilatory assistance before LOC. Although  $E'_{\text{CO}_2}$  was kept below 6 kPa in all patients, it cannot be excluded that in some,  $\text{CO}_2$  retention had an impact on indices. Severe hypercapnia ( $E'_{\text{CO}_2}$  9 kPa, arterial  $\text{CO}_2$  19 kPa) was shown to be accompanied by a decrease in the BIS index.<sup>17</sup> Also, ventilatory assistance, although gently applied, may interfere with the assessment of sedation and indices. However, episodes of hypoventilation occurred in both age categories, and they reflected the clinical reality of our model.

Finally, 20 elderly and 10 young patients presented at least one episode of arterial hypotension during the study period. Arterial hypotension and concomitant bradycardia, for instance, during vasovagal syncope, were shown to be accompanied by a decrease in the BIS index.<sup>18</sup> It cannot be excluded that in some patients, indices were lower than usual due to arterial hypotension.

Our findings are clinically relevant for two reasons. First, differences in indices between the two age groups at LOC were between 15 and 20 u for all monitors; this is not marginal. Secondly, at LOC, most elderly patients were largely outside the 'safe' index-range (i.e. 40–60). Early work in healthy volunteers (mean age, 31 yr) suggested that the BIS index correlated well with the effects of propofol, midazolam, or isoflurane on the level of consciousness and recall, and that BIS levels  $< 50$  indicated that a participant was probably unconscious and will have no recall.<sup>19</sup> Subsequently, a range of 40–60 was recommended for all types of general anaesthesia and independent of whether i.v. or volatile anaesthetics were used.<sup>20</sup> This range was also applied in large clinical trials to ensure adequate depth of anaesthesia.<sup>21–22</sup> For instance, the B-Aware trial investigators postulated that with BIS

values of  $\leq 55$ , awareness could be avoided.<sup>21</sup> However, in our study, between 77% (SE) and  $> 94\%$  (BIS) of elderly patients lost consciousness at indices of  $\geq 60$ . Although our findings should not be directly extrapolated to patients undergoing surgery with painful stimulation, our data suggest that the maintenance of the standard 40–60 index range in elderly patients throughout surgery may result in unnecessary and potentially harmful overdosing of anaesthetics with the subsequent risk of haemodynamic instability and prolonged awakening time. Inappropriate anaesthesia depth (BIS index  $< 45$ ) was shown to be a predictor of 1 yr mortality after non-cardiac surgery.<sup>23</sup>

In conclusion, in adults undergoing propofol induction, age influences BIS, SE, and RE indices. At LOC, elderly patients have significantly higher indices compared with young patients and in most elderly, values at LOC are well above the recommended 40–60 range for adequate depth of anaesthesia. Processed EEG monitors have been proposed as non-invasive tools to target the administration of anaesthetics, to avoid overdosing that may lead to haemodynamic instability and prolonged awakening time, and to prevent underdosing with the subsequent risk of intra-operative awareness.<sup>20–24–25</sup> Our data suggest that when using these monitors, specific, age-related 'safe' limits of the respective indices should be defined for young and elderly patients.

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